CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DAZOMET

Chemical Code # 000233, Tolerance # 50466
SB# 621

February 6, 1995

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, **possible adverse effect**
Oncogenicity, rat:	Data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	Data gap, no adverse effect
Teratology, rabbit:	No data gap, **possible adverse effect**
Gene mutation:	Data gap, no adverse effect

Chromosome effects: Data gap, **possible adverse effect**

DNA damage: Data gap, no adverse effect

Neurotoxicity: Study not required at this time

Toxicology one-liners are attached.

All record numbers through 132456 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T950206
T. Moore, 2/6/95

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

026 114694, "Report on the Oral Toxicity of Dazomet in Rats after 24 Months Administration in the Diet", (Dr. B. Kunbroth, BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen, W. Germany, Report # 89/0276, 31 July 1989); Dazomet Technical (purity: 98.2%); 20 Wistar (Chbb = THOM (SPF) rats/sex/group; Dose: 0, 5, 20, 80, 320 ppm in the diet for 24 months (males: 0, 0.3, 1, 4, or 18 mg/kg/day, females: 0, 0.3, 1, 6, or 23 mg/kg/day); No apparent treatment-related mortality; Clinical Observations: marginal reduction in bodyweights (M/F: 320 ppm), no other treatment-related effects; Hematology: decreased numbers of rbc's and concentration of hemoglobin (F: 320 ppm, day 92, 184, 373, 555); Clinical Chemistry: reduced serum cholinesterase activity (F: 80, 320 ppm, day 92; 320 ppm, day 184, 373), reduced levels of total protein (F: 80, 320 ppm, day 92; 320 ppm, day 373, 555), albumin (F: 80, 320 ppm day 92; 320 ppm, day 373), and globulin (F: 80, 320 ppm, day 92; 320 ppm, day 184, 373), reduced creatine level (F: 80, 320 ppm, day 92; 320 ppm, day 373, 723); Necropsy: increased relative liver weight (M: 320 ppm), decreased kidney weight (M/F: 320 ppm); Histopathology: increased incidence and severity of heptocellular fat deposition and vacuolation and altered cell foci (F: 320 ppm); **Adverse effects are not indicated; **Nominal Chronic NOEL**: 80 ppm (based upon hematological and clinical chemical effects and liver vacuolation in the females in 320 ppm treatment group); **Acceptable.** (H. Green and T. Moore, 11/23/94).

CHRONIC TOXICITY, DOG

****028 114704**, "Report on the Study of Toxicity of Dazomet in Beagle Dogs via the Diet over 12 Months", (Dr. J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen, W. Germany, Report # 89/0050, February 1989); Dazomet technical (purity: 98.2%); 6 Beagle dogs/sex/group; Nominal Doses: 0, 15, 50, or 150 ppm in the diet for 12 months, (0, 0.5, 1.6, or 4.8 mg/kg/day); No mortality; Clinical observations: marginal decrease in bodyweight gain (M/F, 150 ppm); Hematology: no treatment-related effects; Clinical Chemistry: elevated levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (M/F, 150 ppm); No treatment-related effects in urinalysis or ophthamology; Necropsy: increased mean relative liver weight (M, 150 ppm), focal or diffuse discoloration of liver (F, 150 ppm); Histopathology: moderate to severe chronic hepatitis, severe cirrhosis (M/F, 150 ppm), iron-positive pigment deposition increase (M/F, 50, 150 ppm), testicular tubular atrophy in 2 of 6 (M, 150 ppm); **Possible adverse effect**: testicular tubular atrophy; **NOEL:** 50 ppm (based upon effects on serum enzymes, liver and testicular histopathology in 150 ppm group); **Acceptable.** (H. Green and T. Moore, 11/28/94)

ONCOGENICITY, RAT

030 114700, "Report on the Oncogenic Potential of Dazomet in Rats after 24 Month Administration in the Diet", (Dr. B. Kuhbroth, BASF Aktiengesellschaft, Department of Toxicology, D6700 Ludwigshafen, W. Germany, Report # 89/0277, July 1989); Dazomet technical (purity: 98.2%); 50 Wistar (Chbb = THOM (SPF) rats per sex per group received nominal doses of 0 (ground Kliba 343 rat/mouse/hamster maintenance diet), 5, 20, and 80 ppm in the diet for 24 months (males: 0, 0.27, 1.08, 4.43 mg/kg/day, females: 0.35, 1.37, 5.66 mg/kg/day); No treatment-related mortality; Clinical Observations: no treatment-related signs, no effect upon food consumption or body weight gain; Necropsy: no effect upon organ weights, apparent enlargement of spleen and iliac lymph nodes (20, 80 ppm); Histopathology: slight increase in diffuse fat deposition (80 ppm, M), altered cell foci and basophilic cell foci (80 ppm, F) in the liver, no treatment-related increase in tumor incidence; **No adverse effects are indicated**; **Chronic and oncogenic NOEL** $\geq$ 80 ppm; **Unacceptable**, possibly upgradeable (no treatment-related effects apparent in the high dose group, dosing rationale is unclear). (H. Green and T. Moore, 11/22/94).

ONCOGENICITY, MOUSE

** 029 114705, "Report on the Study of the Oral Toxicity of Dazomet in Mice after 78 Week Administration in the Diet", (Dr. B. Kunbroth, BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen, W. Germany, Report # 89/0341, September 1989); Dazomet technical (purity: 98.2%); 50 B6C3F1 mice/sex/group (main study); Nominal Doses: 0 (ground Kliba 343 maintenance diet), 20, 80, 320 ppm for 78 weeks; (satellite group) 10 animals/sex/group, treated at the same levels for 52 weeks; (Males: 0, 4, 16, or 68 mg/kg/day, females: 0, 6, 22, or 93 mg/kg/day); No treatment-related mortality; Clinical Observations: no treatment-related effects; Hematology: no treatment-related effects; Necropsy: increased mean liver weight (M/F, 320 ppm, 52, 78 weeks), decreased mean kidney weight (M, 320 ppm, 52 weeks, 20, 80, 320 ppm, 78 weeks), increased number of liver masses and foci (F, 320 ppm, 78 weeks); Histopathology: increased hepatocyte lipid deposition (M/F, 320 ppm, 52, 78 weeks), increase

in basophilic foci in liver (F, 320 ppm, 78 weeks), increased hemosiderin deposition in the spleen (M/F, 320 ppm, 52, 78 weeks), increased extra-medullary splenic hemopoiesis (M/F, 320 ppm, 78 weeks), increased incidence of heptacellular adenomas (F, 320 ppm, 78 weeks) (p=0.159, Fisher Exact Test, p=0.0475 for Cochran Armitage trend test); **Adverse effects are not indicated**; **Chronic NOEL: 80 ppm** (based on histopathologic effects in the 320 ppm group; **Oncogenic NOEL:** 320 ppm; **Acceptable**. (H. Green and T. Moore, 2/6/95).

REPRODUCTION, RAT

027 114698, "Report on the Reproduction Study with Dazomet in Rats; Continuous Dietary Administration Over 2 Generations (2 Litters in the First and 1 Litter in the Second Generation)", (Dr. J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen, W. Germany, Report # 89/0051, February 1989); Dazomet technical (purity: ≥ 97.0%); 24 Wistar (Chbb = THOM (SPF)) rats/sex/group; Nominal Dose: 0 (Kliba 343 feed), 5, 30, or 180 ppm in the diet through 2 generations (with 2 litters in the first generation and 1 in the second) (Males: 0, 0.46, 2.75, or 17.0 mg/kg/day, females: 0, 0.52, 3.15, or 19.0 mg/kg/day); No parental mortality; Clinical Observations: reduction in parental bodyweight gain (M/F, 180 ppm, F0 and F1); Clinical Chemistry: Reductions in alanine aminotransferase (M/F, 180 ppm, F0); Necropsy: increased relative mean liver weight (M/F, 180 ppm, F0 and F1); Histopathology: increased incidence and severity of fatty changes in liver (M, 180 ppm, F0 and F1); No apparent effects on reproduction; **Adverse effects are not indicated; **Systemic Parental NOEL:** 30 ppm (based upon increased incidence and severity of fatty changes in the liver of the 180 ppm group; modest decrease in body weight gain), **Reproductive NOEL≥** 180 ppm; **Acceptable**. (H. Green and T. Moore, 11/30/94)

TERATOLOGY, RAT

031 114702, "Report on the Study of Prenatal Toxicity of Dazomet After Oral Administration (Gavage)", (Dr. J. Hellwig and Dr. B. Hildebrandt, BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen, West Germany, Report # 87/0457, December 1987). Dazomet with ≥ 97.0% purity was used as test article. 25 mated female Wistar (Chbb = THOM (SPF)) rats received nominal doses of 0 (olive oil), 3, 10, and 30 mg/kg/day by gavage on gestation days 6 through 15. **Adverse effects are not indicated**. Maternal NOEL **=** 10 mg/kg/day (reduced food consumption and body weight gain at the high dose level). Developmental NOEL = 30 mg/kg/day. **Unacceptable** and upgradeable with submission of dosing material analyses for content. (H. Green and T. Moore, 11/10/94).

TERATOLOGY, RABBIT

032 114706, "Study to Determine the Prenatal Toxicity of Tetrahydro-3,5-Dimethyl-2H-1,3,5-thiadiazine-2-thione (= Dazomet) in Rabbits", (J. Merkle, Department of Toxicology, BASF Aktiengesellschaft, West Germany, Report # 80/0053, 3 March 1980). Dazomet with ≥ 98% purity was used as test article. 15 mated female Himalayan, Chbb: HM (selective breeding) rabbits per group received 0 (carboxymethyl cellulose), 6.25, 12.50, and 25.00 mg/kg/day by gavage on gestation days 6 through 18. (Maternal) No mortality; no apparent treatment-related effects; Necropsy: no treatment-related lesions; (Developmental) increased number of early resorptions (25 mg/kg/day); **Possible adverse effects:** increased incidence of early resorptions**; Maternal NOEL:** 25 mg/kg/day; **Developmental NOEL:** 12.5 mg/kg/day (based on the increased incidence of early resorptions in the 25.0 mg/kg/day group); **Unacceptable** and not upgradeable (no analysis of dosing material, inadequate method of fetal evaluation). (H. Green and T. Moore, 11/21/94).

033 114707, "Study to Determine the Prenatal Toxicity of Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione (= Dazomet) in Rabbits", (J. Merkle, Department of Toxicology, BASF Aktiengesellschaft, West Germany, Report # 80/0037, 10 January 1983); Dazomet technical (purity: ≥ 98%); 11 to 14 mated female Himalayan Chbb: HM (outbred strain) rabbits per group received 0 (carboxymethyl cellulose), 25.0, 50.0, and 75.0 mg/kg/day by gavage on gestation days 6 through 18, an untreated control group was also used; (Maternal) 2 animals died (75 mg/kg/day); Clinical Observations: reduced food consumption and body weight gain (75 mg/kg/day); Necropsy: no treatment-related lesions; (Developmental): increased incidence of fetal resorptions (50 and 75 mg/kg/day); **Possible adverse effect:** increased incidence of fetal resorptions; **Maternal NOEL:** 50 mg/kg/day (reduced food consumption and body weight gain in the 75 mg/kg/day group); **Developmental NOEL:** 25 g/kg/day (based on the increased incidence of fetal resorptions in the 50 mg/kg/day group; **Unacceptable** and not upgradeable (no analysis of dosing material provided, fewer than 12 pregnant dams per group, inadequate method used for skeletal exam). (H. Green and T. Moore, 11/21/94)

**** 046 132456**; "Study of the Prenatal Toxicity of Dazomet in Rabbits after Oral Administration (Gavage)," J. Hellwig; 833; Himalayan Rabbit; BASF Aktiengesellschaft, Department of Toxicology, D-67056 Ludwigshafen, Germany; Project No. 40R0062/92058; 9/93; Dazomet Technical (batch no. 92-1) (purity: 98.0%); 15 females/dose; Doses: 0 (0.5% carboxymethyl cellulose), 5, 15, 45 mg/kg/day for days 7 through 19 of post-insemination, by gavage; Mortality: 1 dam (45 mg/kg/day) on day 9; Clinical Observations: significant decrease in body weight gain of dams from day 7 to day 19 (45 mg/kg/day), blood in bedding of 2 dams starting on day 22 (45 mg/kg/day); Necropsy: (Maternal) significant decrease in mean uterine weight, reduced body weight gain (45 mg/kg/day), (Developmental) increased number of early resorptions, increased incidence of fetal skeletal variations (45 mg/kg/day); **Adverse effect:** increased incidence of fetal resorptions; **Maternal NOEL:** 15 mg/kg/day (based upon decreased body weight gain and mean uterine weight in 45 mg/kg/day group); **Developmental NOEL:** 15 mg/kg/day (based upon increased number of early resorptions and increased incidence of fetal skeletal variations in the 45 mg/kg/day group); Study acceptable. (Moore, 10/26/94)

GENE MUTATION

006 038471, "Mutagenicity Evaluation of Sample #100, Final Report", (David J. Brusick, Ph.D., Litton Bionetics, Inc., Kensington, MD., Report # T6081, 26 October 1976). The test article, designated Sample #100, was described as a white powder. Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 and Saccharomyces cerevisiae strain D4 were exposed to concentrations of 0 (DMSO), 0.10, 1.00, 10.00, 100.00, and 500.00 µg/plate in the presence and absence of activation (Aroclor-induced rat liver microsomal enzyme preparation) for 48 hours. **Increased reversion frequency is not indicated**. **Unacceptable** and not upgradeable (no replicates, no dosing rationale). (H. Green and T. Moore, 12/12/94).

006 038472, "Mutagenicity Evaluation in Salmonella Typhimurium", (Jenness B. Majeska, The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT., Report # T-10044, 9 June 1980). The test article is identified as N-521, EHC-0008-7-7 and described as a white powder. Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed for 48 hours to concentrations of 0 (DMSO), 3.7, 11.1, 12.3, 33.3, 37.0, 100.0, 111.1, 300.0, 333.3, or 1000.0 µg/plate in the presence and absence of activation. **Increased reversion frequency is not indicated**. **Unacceptable** and upgradeable with individual plate data, and test article analyses. (H. Green and T. Moore, 12/12/94).

006 038475, "Mutagenicity Evaluation of N-521 in the In Vitro Transformation of BALB/3T3 Cells Assay", (Dale W. Matheson, Litton Bionetics, Inc., Kensington, MD., Report # T-6412, June 1978). Test article is identified as N-521. BALB/3T3 mouse cells were exposed for 72 hours at 0 (DMSO), 0.078, 0.156, 0.312, 0.625, and 1.250 µg/ml. 9 to 10 replicates per dose level were used. **Increased frequency of cell transformation is not indicated**. **Unacceptable**, not upgradeable (test article/dosing material analyses and cytotoxicity results are not included, no activation).
(H. Green and T. Moore, 12/13/94).

006 038478, "Mutagenicity Evaluation of N-521 Technical, Batch # 149 in the Sex-Linked Recessive Lethal Test in Drosophila melanogaster", (E. Sky Benson, Litton Bionetics, Inc., Kensington, MD., Report # T-10012, July 1979). The test article is identified as N-521 technical. 200 Drosophila melanogaster males per group received 0 (DMSO), 0.025, and 0.050 mg/ml in sucrose solution. 874 to 2453 chromosomes were tested per brood. **An increase in forward mutations is not indicated**. **Unacceptable** and upgradeable (test article/dosing material analyses, results of dose range study, and numbers of non-fertile males). (H. Green and T. Moore, 12/13/94).

CHROMOSOME EFFECTS

006 038473, "Mutagenicity Evaluation of N 521 in an In Vitro Cytogenetic Assay Measuring Sister Chromatid Exchange and Chromosome Aberrations", (Daniel Stetka, Litton Bionetics, Inc., Kensington, MD, Report # T-6410, March 1979). The test article is identified as N-521. Fisher L5178Y lymphoma cells received a 4-hour exposure to untreated (medium), 0 (DMSO), 1.56, 3.13, 6.25, 12.50, and 25.00 ng/ml in the presence and absence of activation. **A slight increase in chromosomal aberrations is indicated**. **Unacceptable** and upgradeable with the submission of test article identity, explanation of dosing rationale, and cytotoxicity results). (H. Green and T. Moore, 12/13/94).

006 038474, "N-521 Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test", (Jenness B. Majeska, M.S., The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT. 06032, Report # T-10136, 20 November 1980). The test article is identified as N-521, EHC-0008-7-7. Fischer mouse L5178Y (TK+/-) lymphoma cells were assayed for forward gene mutation, chromosomal aberrations, and sister chromatid exchanges. They received 4 hour exposure to medium, 0 (DMSO), 0.15, 0.46, 0.60, 0.80, 1.00, 1.37, 2.00, 3.00, 4.00, 4.12, 5.00, 6.00, 8.00, 10.00, 12.35, 20.00, 30.00, 37.04, or 111.11 µg/ml in the presence and absence of activation. **Increased forward mutation and chromosomal aberration are indicated. Unacceptable** and upgradeable (test article identification, number of cultures per assay). (H. Green and T. Moore, 12/13/94).

006 038477, "Mutagenicity Evaluation of N-521 in the Rat Bone Marrow Cytogenetic Assay", (Daniel Stetka, Litton Bionetics, Inc., Kensington, MD., Report # T-10011, July 1979). The test article is identified as N-521. 8 or 24 male Sprague-Dawley albino rats, strain CRL:COBS (SD) BR, per group received single and multiple (5 treatments, 24 hours apart) exposures by gavage at 0 (distilled water), 6, 20, and 60 mg/kg. Sampling occurred 6, 24, or 48 hours after the final treatment. **An increase in chromosomal aberrations is not indicated**. **Unacceptable** and not upgradeable (used males only with no justification, inadequate dosing rationale). (H. Green and T. Moore, 12/13/94).

DNA DAMAGE

006 038476, "N-521, Morphological Transformation of BALB/3T3 Cells", (Jenness B. Majeska, The In Vitro Toxicology Section, Environmental Health Center, Stauffer Chemical Company, Farmington, CT., Report # T-10137, 5 December 1980). The test article is identified as N-521, EHC-0008-7-7. BALB/3T3 mouse cells were exposed for 72 hours to medium, 0 (DMSO), 0.025, 0.050, 0.100, 0.200, and 0.400 µg/ml with 15 replicates per dose level. **Increased frequency of cell transformation is not indicated. Unacceptable** and not upgradeable (no activation of the test material included in the study). (H. Green and T. Moore, 12/13/94).

NEUROTOXICITY

No study submitted.